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Attorney Docket No. 03037.000100

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

SHIGEAKI HARAYAMA ET AL.

Application No.: 09/742,123

Filed: December 22, 2000

For: SYNTHESIS OF HYBRID POLYNUCLEOTIDE MOLECULES USING SINGLE-STRANDED POLYNUCLEOTIDE MOLECULES

Examiner: Arun K. Chakrabarth

Group Art Unit: 1655



May 17, 2002

Commissioner for Patents
Washington, D.C. 20231

AMENDMENT AND PETITION FOR EXTENSION OF TIME

Sir:

Applicants petition to extend the time for response to the Office Action dated November 23, 2001 to May 23, 2002. A check in the amount of $920.00 for payment of the extension fee is enclosed. Please charge any additional fee required for the extension, and credit any overpayment, to Deposit Account 06-1205.

In response to the Office Action dated November 23, 2001 (Paper No. 6), please amend the application as follows:

IN THE ATTORNEY DOCKET NUMBER

Please change the Attorney Docket Number to --03037.000100--.

IN THE CLAIMS:

Please cancel Claim 3 without prejudice or disclaimer.

Please amend Claims 1, 2, 4 and 5 and add new claims 6-10 to read as follows. A marked-up copy of these claims, showing the changes made thereto, is attached.

1. (Amended) A method for making libraries of hybrid polynucleotide molecules comprising the steps of:

selecting a first single-stranded polynucleotide which corresponds to a coding strand of a first family gene;

selecting a second single-stranded polynucleotide which corresponds to a non-coding strand of a second family gene;

fragmenting the first and second single stranded polynucleotides to form polynucleotide fragments;

hybridizing the polynucleotide fragments to form heteroduplex molecules; and

conducting nucleotide elongation on the heteroduplex molecules, wherein said single-stranded polynucleotide molecules are used as starting materials.

2. (Amended) The method of claim 1, wherein the first family gene is different from the second family gene and wherein the first single-stranded polynucleotide comprises at least one homologous sequence and at least one sequence which is heterologous to the second single-stranded polynucleotide.

3. Cancelled.

4. (Amended) The method of claims 1 or 2, wherein mutations are introduced into hybrid polynucleotide molecules.

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5. (Amended) A method for making libraries of hybrid polynucleotide molecules, which comprises:

(i) preparing two single-stranded polynucleotide molecules comprising sequences which are complementary to each other,

(ii) fragmenting the two single-stranded polynucleotide molecules,

(iii) incubating the fragmented molecules under conditions such that hybridization of fragmented polynucleotide molecules occurs and *de novo* polynucleotide synthesis on the hybridized molecules occurs,

(iv) denaturing the resultant elongated double-stranded polynucleotide molecules into single-stranded polynucleotide molecules,

(v) incubating the resultant single-stranded polynucleotide molecules under conditions such that hybridization of single-stranded polynucleotide molecules occurs and *de novo* polynucleotide synthesis on the hybridized molecules occurs, and

(vi) repeating at least two further cycles of steps (iv) and (v).

6. (New) The method of claims 1 or 5, wherein at least one of the two single-stranded polynucleotide molecules is fragmented randomly.

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7. (New) The method of claims 1 or 5, wherein both of the two single-stranded polynucleotide molecules is fragmented randomly.

8. (New) The method of claims 1 or 5, wherein mutations are introduced into at least one of the first and second single-stranded polynucleotides prior to production of the heteroduplex molecules.

9. (New) The method of claims 1 or 5, wherein mutations are introduced into both of the first and second single-stranded polynucleotides prior to production of the heteroduplex molecules.

10. (New) The method of claim 2, wherein said homologous sequence is at least 15 bases.

REMARKS

Claims 1 and 2 have been amended in order to recite the present invention with the specificity required by statute. Additionally, Claim 3 has been cancelled as superfluous and new Claims 6-10 are presented in order to more specifically recite various preferred embodiments of the present invention. The subject matter of the amendment may be found in the original claims as well as in the specification as filed, e.g., at page 16, lines 13-15. Accordingly, no new matter has been added.

Claims 1-5 are rejected under 35 U.S.C. §112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps and as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In response, the claims have been amended in order to address the Examiner's noted concerns. Accordingly, this rejection should now be mooted and withdrawal thereof is earnestly solicited.

Claims 1-5 are rejected under 35 U.S.C. §102(e) as being anticipated by Stemmer U.S. Patent No. 6,180,406. In support of this rejection, the Examiner states that

> Stemmer teaches a method for making libraries of hybrid polynucleotide molecules in which double-stranded polynucleotide molecules are not used as starting materials.

This rejection is respectfully traversed. However, prior to setting forth their bases of traversal, Applicants would like to briefly set forth the salient features of the present invention and, *inter alia*, its patentable nature over the prior art.

As the Examiner is aware, the present invention (as recited in claim 1) relates to a method of making libraries of hybrid polynucleotides using two single-stranded polynucleotides, fragmenting the two single-stranded polynucleotides, hybridizing the fragments to form heteroduplex molecules and conducting nucleotide elongation on the heteroduplex molecules. Claim 5 is similar but differs, in part, in that once a pair of complementary single-stranded polynucleotides are fragmented, the fragments are incubated under conditions to obtain both hybridization and *de novo* polynucleotide synthesis.

Simply put, these features are neither taught nor suggested by the prior art.

Stemmer describes a method for virus-plasmid recombination in which starting material is cloned into vectors (see column 54 at lines 14-15 where Stemmer teaches "[t]he initial substrates for recombination are cloned into both plasmid and viral

vectors"). Although the starting material may be single-stranded phage DNA (see column 55, lines 5-8), Stemmer does not teach or suggest fragmentation of the starting material.[1/]

The Examiner further notes at page 5, lines 14-16 of the Office Action that Stemmer teaches

> (ii) randomly or non-randomly fragmenting the two single-stranded polynucleotide molecules (Example 14, Column 87 lines 8-12). This step is inherently carried out by heating the reaction mixture to 70 degree centigrade and cooling.

However, at no place in the referred text is single-stranded DNA fragmented; rather, all fragments are made synthetically. Nor does heating to 70 degrees and cooling accomplish any fragmentation. Instead, those laboratory steps merely promote the annealing of DNA, in this case the single-stranded template to the synthetic oligos.[2/]

Accordingly, it is seen that the Examiner has not made out a prima facie case of anticipation, regarding e.g., original claim 3 and, accordingly, amended claims 1 and 5. For this reason at least, if the Examiner now addresses this deficiency in the record, the next Official Action must not be made "final".

In view of the above amendments and remarks, Applicants submit that all of the Examiner's concerns are now overcome and the claims are now in allowable condition. Accordingly, reconsideration and allowance of this application is earnestly solicited.

Claims 1, 2 and 4-10 remain presented for continued prosecution.

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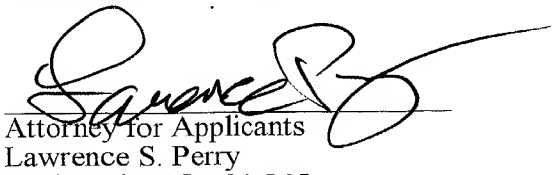
1/ In this regard, Stemmer describes from column 86, line 39 to column 88 line 3 a protocol for single-stranded mutagenesis wherein oligonucleotides are synthetic, e.g., not fragmentated, as readily as understood by use of the term "degenerate codons", since the skilled artisan cannot fragment something to become degenerate.

2/ Additionally, while the Examiner points to Stemmer Claims 11 and 12, such claims clearly utilize double-stranded starting material: ("the cleavage of said polynucleotides into random double-stranded fragments") and so, are essentially irrelevant to the subject matter of the present invention.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

Respectfully submitted,



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